

REMARKS

Favorable reconsideration and allowance of this application are requested.

1. Request for Continued Examination

As a procedural note, the present amendment is being filed concurrently with a formal Request for Continued Examination (RCE) under 37 CFR §1.114. Accordingly withdrawal of the "finality" of the June 22, 2010 Official Action is in order so as to allow entry and consideration of the amendments and remarks presented herewith.

2. Change of Address and Power of Attorney

The Examiner's attention is directed to the change of address and new power of attorney filed in the subject application. The Examiner's assistance to ensure that the Office's records are changed to ensure that all future official communications are dispatched to the undersigned at the new address of record will be appreciated.

3. Discussion of Amendments

By way of the amendment instructions above, non-elected claims 17-25 have been canceled without prejudice to the applicant's rights under 35 USC §121.

Independent claims 1 and 26 have also been amended in an effort to address the informalities that have raised and to clarify that an amount of the mixture is in an amorphous state sufficient to achieve a stable crystalline/amorphous matrix and obtain a reduced hygroscopicity of the formulation of less than 5% by weight after 8 hours in a 75% relative humidity environment. Support for such an amendment can be found in the published specification at paragraph [0029]. Claims 12-14 have thus been canceled as redundant.

Therefore, following entry of this amendment, claims 1-11, 15-16 and 26-30 will remain pending herein for which favorable reconsideration and allowance are requested.

4. Response to Claim Objections

The amendment to claim 1 deleting the limitation of from 0.1 to 10% by wt of additive/stabilizer therefrom and providing for an open-ended preamble (i.e., by changing “consisting of” to “comprising”) renders moot the objections advanced against prior claims 8 and 9.

5. Response to 35 USC §112 Rejections

A. 35 USC §112, First Paragraph Rejection

Applicants are perplexed by the Examiner’s rejection of claims 1-16 and 26-30 under 35 USC §112, first paragraph. Specifically, applicants know of no statute or rule whereby each and every feature of a claimed invention must be shown in an example. Instead, what must be disclosed in an applicant’s specification is sufficient description to convey to those skilled in the art that the applicant was in possession of the claimed invention. See, *In re Gosteli*, 19 USPQ2d 1614, 1618 (Fed. Cir. 1989) and *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

As the Examiner acknowledges, there is unquestionably disclosure that “from 0.1 to 10% by wt. of additive/stabilizer” is present in paragraph [0046] of the applicant’s published specification. The fact that it is disclosed as being an optional instead of a required component is irrelevant to an analysis under 35 USC §112, first paragraph. The point is, that a skilled person is provided with a description that such a material in the stated amount can be incorporated into the formulation if desired.

Withdrawal of the rejection advanced under 35 USC §112, first paragraph is therefore in order.

B. 35 USC §112, Second Paragraph Rejections

The amendments made to the claims above are believed to address the issues raised by the Examiner under 35 USC §112, second paragraph thereagainst. Withdrawal of such rejections is also believed to be in order.

6. Response to 35 USC §102(b) Rejection

Claim 26 attracted a rejection under 35 USC §102(b) as allegedly anticipated by Maa (WO 02/101412). Applicants respectfully disagree.

In this regard, pending claim 26 is directed to a powdered formulation which is a shelf freeze-dried mixture. Batch 156-35-1 of Maa which is disclosed at page 60, Table 2.9 is described at page 61 lines 3-4 to have been prepared by “the SFD process”. The SFD process is disclosed at page 52 line 27 to page 55 line 6 as being a spray freeze drying process. Maa does not disclose shelf freeze drying. Accordingly, claim 26 is not anticipated by Maa.

7. Response to 35 USC §103(a) Rejections

The only issue remaining to be resolved in this application is the Examiner’s rejection of prior claims 1-16 and 26-30 under 35 USC §103(a) as allegedly “obvious”, and hence unpatentable, over Maa in view of Chen (*J. Pharm. Biomed. Anal.*, 26, 2001). Applicants respectfully suggest that neither Maa nor Chen is appropriate as a reference against the amended pending claims herein.

In this regard, Maa fails to teach a stable formulation of a sensitive active material having reduced hygroscopicity. In particular, while there is disclosure in Maa that an excipient can “maintain low hygroscopicity”, there is no disclosure in Maa of

what excipient has such function. In contrast, according to the present invention, it has surprisingly been found that a stable, reduced hygroscopicity formulation of a mixture of a sensitive active material and an excipient can be obtained if from 0.1 to 50% by weight of the mixture is in an amorphous state. Such a finding would not have been obvious from a combination of Maa (which offers no relevant teaching) and Chen because Chen states at page 64, column 1 lines 3-5 that: "[t]he relatively high free energy of an amorphous form results in higher ... hygroscopicity." (emphasis added)

The Examiner refers to the disclosure at page 26 lines 17-27 of Maa as allegedly teaching crystalline and amorphous excipients for use in stabilizing the active material. However, this referenced disclosure of Maa does not offer a teaching which is relevant to the presently claimed invention. Applicant acknowledges that at page 26, lines 17 to 19, Maa states that: "[t]he excipients chosen for use in the present invention may serve specific functions such as protein stabilization or surface protection or may be used as bulking agents or to maintain low hygroscopicity of the powders." However, Applicant notes that there is no disclosure in Maa of which excipients may be used to achieve the functions of producing a stable formulation (not just a stable protein) and maintaining low hygroscopicity. Therefore, the subject matter of the claims is not obvious over Maa or Maa in view of Chen.

In contrast to the Examiner's assertion, the excipients listed at page 26, lines 20-22 (which are amorphous or crystalline saccharides, polymers or amino acids or physiologically acceptable salts thereof) and at page 26 lines 25-26 (which are monosaccharide, disaccharide or higher oligo- or poly-saccharide) are said at page 26 lines 22-24 to *allow the particles to collapse and densify*. This is most certainly is not a teaching relevant to the presently claimed invention. Moreover Applicant could not identify a teaching at page 26 lines 17-27 of Maa of a specific excipient which stabilizes the active material, contrary to the Examiner's assertion. Therefore, it would not have been obvious at all to try the excipients disclosed at page 26 lines 17-27 to produce a

stable composition which has reduced hygroscopicity as there is no disclosure or suggestion that the disclosed excipients even have such a function.

Examiner refers to the disclosure at page 27 lines 8-12 and claim 7 of Maa as teaching excipients which are covered by claims 1, 6 and 7 of the present application. At page 27 lines 10-12, it is stated that the excipients disclosed at page 27 lines 8-10 are capable of stabilizing proteins used as pharmaceutical agents during the spray freeze drying process and during long term storage. There is no disclosure in Maa of such excipients stabilizing the formulation or reducing hygroscopicity. Indeed, it would be expected that an amorphous excipient would increase hygroscopicity from the teaching of Chen at page 64, column 1 lines 3-5 that “[t]he relatively high free energy of an amorphous form results in higher ... hygroscopicity”. (emphasis added) Therefore, it would not have been obvious at all to try the excipients disclosed at page 27 lines 8-12 to produce a stable composition which has reduced hygroscopicity as there is no disclosure or suggestion that the disclosed excipients have such a function.

The Examiner argues that Maa teaches the addition of a surfactant at page 28 lines 8-9 “for stabilizing the active material”. Applicant notes that page 28 lines 8-9 is as follows: “[t]his combination of excipients is preferably used together with a surfactant which is typically present in an amount of from 1 to 5 % by weight”. Therefore there is no statement of the function of the surfactant at page 28 lines 8-9, contrary to the Examiner’s assertion. Therefore, it would not have been obvious to try the surfactant disclosed at page 28 lines 8-9 to produce a stable composition which has reduced hygroscopicity as there is no disclosure or suggestion that the surfactant has such a function.

The Examiner also argues that Maa teaches the addition of 0.1% methionine in formulation 156-16-2 at page 57. Applicant notes that that formulation is disclosed as containing methionine but there is no teaching in Maa about the purpose of including

methionine. Without knowing why to include methionine in a formulation, it is respectfully submitted that it would not be obvious to try including it.

Examiner argues that Maa teaches at page 26 line 19 that excipients are chosen to maintain low hygroscopicity of the powders. However, there is no disclosure in Maa of which excipients maintain low hygroscopicity. In the absence of such a disclosure, it would not have been obvious to try the excipients claimed in claim 1 to produce a stable composition which has reduced hygroscopicity as there is no disclosure or suggestion in Maa of which excipients have this effect. As noted by the Examiner, Maa identified the problem of reducing the hygroscopicity of powdered formulations but did not solve it.

Examiner argues that Maa at page 28 lines 3-4 teaches amorphous excipients present in an amount from 10 to 90 wt% and a crystalline excipient in an amount from 10 to 90 % by weight. Applicant was unable to find such a disclosure at page 28 lines 3-4 of Maa. Instead, Maa only discloses ranges for an amorphous saccharide and a crystalline saccharide. In claim 1, where the excipient is crystalline, it cannot be a saccharide. Therefore this disclosure at page 28 lines 3-4 of Maa does not offer a teaching relevant to claim 1 or its dependent claims.

In the relatively recent case *KSR Int'l. Co. v. Teleflex Inc. et al*¹ (hereinafter "KSR"), the Supreme Court noted that teaching away by a prior art reference is evidence of *non-obviousness*.²

¹ 550 U.S. 398 (2007)

² "In *United States v. Adams*...a companion case to *Graham*, the Court...relied upon the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art." *KSR, supra.* at 416.

As further noted by the Court in *KSR*,

“Where there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.”³

Here of course there are not a finite number of identified predictable outcomes when one attempts to form stable formulations of a sensitive active material which have reduced hygroscopicity. Instead, according to Chen, there is but one very predictable and deleterious outcome – namely, an increase in hygroscopicity – if one attempts to employ an amorphous material. The fact that the present applicants have discovered that stable, reduced hygroscopicity formulations of a mixture of sensitive active material and an excipient can be obtained if from 0.1 to 50% by weight of the mixture is in an amorphous state is manifestly and surprisingly unobvious in light of Chen’s teaching of increased hygroscopicity when amorphous materials are used.

Therefore, this explicit teaching by Chen would not direct an ordinarily skilled person to the presently claimed invention even in view of Maa since the art has been provided with an *explicit* admonition not to use amorphous materials if stable formulations of a mixture of sensitive active material and an excipient having reduced hygroscopicity may be desired.

In view of the above analyses, therefore, Applicant respectfully suggests that the rejection advanced under 35 USC §103(a) must be withdrawn and that all pending claims herein are in condition for prompt allowance.

³ *KSR, supra.* at 421.

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8. Fee Authorization

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140.

Respectfully submitted,

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